Remarks

In view of the above amendments and the following remarks, reconsideration of the grounds of rejection set forth in the outstanding office action is respectfully requested.

This submission is accompanied by a Request for Continued Examination, a Declaration of Henry Nicolas Jabbour under 37 C.F.R. § 1.132 ("Jabbour Decl."), and a Petition for Five-month Extension of Time. All fees associated this submission can be charged to Deposit Account 14-1138. Any deficiencies and any overpayment can also be applied to this same account.

New claim 32 has been introduced, specifying that the FP receptor antagonist blocks Gq coupling and generation of inositylphosphate. Descriptive support for this limitation appears at page 6, lines 10-14, of the present application. Therefore, no new matter has been introduced by new claim 32.

Claims 1, 3-5, 9, 12, 13, and 32 are pending. Claim 32 reads on the elected species, and therefore should be examined together with the remaining claims.

Applicants respectfully submit that the objection to the specification (and sequence listing submitted on April 9, 2007) is improper. The sequences of Table 1 (page 8 of the application) for which no sequence identifier is provided are only those that appear in uppercase letters. As noted at page 7, lines 25-26, of the specification, uppercase letters represent D-amino acids. The sequence listing requirements of 37 C.F.R. § 1.821 are not intended to embrace amino acid sequences that contain D-amino acids. Therefore, no amendments to the sequence listing or specification are required.

The sequence listing and statement pursuant to 37 C.F.R. § 1.821 were filed on April 9, 2007, and the available PAIR records reflect their receipt. If the U.S. Patent and Trademark Office ("PTO") has misfiled its electronic record of the sequence listing, then applicants respectfully request that the examiner contact the undersigned attorney for a replacement.

The rejection of claims 1, 3-5, 9, 12, and 13 under 35 U.S.C. § 112 (first paragraph) for lack of enablement is respectfully traversed.

On pages 4 and 7 of the office action, the PTO asserts that the specification fails to (i) support use of any FP receptor antagonist in the claimed method; and (ii) demonstrate that an FP receptor antagonist can be used to treat a pathological condition of the

uterus associated with abnormal growth of cells of the myometrium or endometrium. Applicants respectfully disagree.

Turning to the first basis of rejection, applicants submit that the present application supports the use of any FP receptor antagonist within the claimed invention. FP receptor antagonists are a pharmacologically well-defined class of molecules which were well known by 2002. Jabbour Decl. ¶ 3. They typically act by binding to the FP receptor and prevent signaling from that receptor as is described on page 6 of the patent application. *Id.* Numerous examples of FP receptor antagonists are described in the patent application. For example, on page 2, lines 10-17, reference is made to Griffin *et al* (1999) *J. Pharmacol. Exp. Ther.* **290**, 1278-1284, which describes the selective FP receptor antagonist AL-8810, and to Sharif *et al* (2000) *J. Pharm. Pharmacol.* **52**, 1529-1539, which describes the FP receptor antagonist AL-3138. *Id.* Dozens of other peptide and non-peptide FP receptor antagonists are described on pages 7 to 11 of the patent application, and many of the references describing these other FP receptor antagonists are incorporated by reference into the specification.

Because all of these FP receptor antagonists, regardless of their structure, are known to possess the same activity, they are functional equivalents for practicing the claimed invention, which involves antagonism of the FP receptor to achieve the therapeutic treatment of a pathological condition of the uterus associated with abnormal growth of cells of the myometrium or endometrium as recited in claim 1.

Other FP receptors beyond those described in the patent application are known, such as AS604872. Jabbour Decl. ¶ 4. AS604872 has been studied by Merck & Co., and in Chollet *et al* (2007) *BMC Pregnancy and Childbirth* 7, S16 ("Chollet") it has been proposed to have therapeutic potential for the treatment of preterm labour in which uterine hyperactivity plays a dominant role. *Id.* The Chollet study, among others, clearly demonstrates the benefit of targeting the FP receptor – specifically its antagonism – as potential therapy in pathophysiology. *Id.* While Chollet does not involve a pathological condition of the uterus as claimed, it certainly confirms the ability to deliver an FP receptor antagonist to achieve therapeutic effect (inhibiting preterm labour). *Id.* Thus, it is reasonable for persons of skill in the art to expect that any molecules that antagonize the FP receptor will be expected to work in the same way, *i.e.*, by blocking the ability of the receptor to be occupied by the natural ligand and to inhibit its ability to signal inside the cell. The same is true for the presently claimed invention.

Thus, the present application fully supports the use of any FP receptor antagonists in the recited methods of treatment.

Turning to the second basis of rejection, applicants submit that the present application fully supports the treatment of a female individual for a pathological condition of the uterus associated with abnormal growth of cells of the myometrium or endometrium, including as uterine carcinoma, endometriosis, and fibroids.

The present application shows for the first time that there is a higher level of expression of the FP receptor in the uterus during the proliferative phase of the endometrium in the menstrual cycle and that expression in uterine carcinoma tissue is significantly elevated compared with normal uterine tissue. Jabbour Decl. ¶ 5. Thus, there is elevated expression of the FP receptor in pathological conditions of the uterus (as is discussed in more detail below). *Id.* When elevated receptor levels are associated with a pathological condition of the tissue or organ in which the elevated receptor levels are found, a credible pharmacological intervention is to inhibit the function of the overexpressed receptor. For example, in many cancers, cell surface receptors such as EGFR are upregulated as the tissue becomes cancerous/metastatic. *Id.* It is a conventional treatment to use a molecule that binds to the receptor (such as the monoclonal antibody Cetuximab in the case of EGFR) to prevent stimulation of the receptor by endogenous ligands. *Id.* Clearly, the overexpression is associated with the pathology, and typically there is additional, undesirable signaling due to the overexpression of the receptor. *Id.* Antagonism of the receptor is able to reduce the undesirable signaling in the pathological condition, which typically is of therapeutic use. *Id.*

Further work performed under Dr. Jabbour's supervision confirms that FP receptor antagonists are useful in treating pathological conditions of the uterus, as described in the patent application. Jabbour Decl. ¶¶ 6, 8. This work is reported in Sales *et al* (2005) *Cancer Res*. **65**, 7707-7716 ("Sales"), which was published after the patent application was filed. Jabbour Decl. ¶ 7. The work reported in Sales builds on the work described in the patent application, noted above, which shows elevated expression of FP receptor in uterine carcinoma. Jabbour Decl. ¶ 8. In particular, the work presented in Sales shows that elevated FP receptor and VEGF expression co-localized in glandular and epithelial cells lining the blood vessels in endometrial (uterine) adenocarcinomas. *Id.* Furthermore, it shows that PGF2α (the natural ligand of the FP receptor) can cause rapid transphosphorylation and activation of the EGF receptor, and activation of MEK signaling *via* the FP receptor resulting in an increase in VEGF promoter activity, expression of VEGF mRNA and secretion of

VEGF protein, all of which are consistent with a role for the FP receptor in stimulating blood vessel formation (angiogenesis) in endometrial (uterine) cancer. *Id.*

These effects of PGF2α on the FP receptor could be abolished by treatment of cells with a specific FP receptor antagonist, AL8810, and similar effects were found when endometrial adenocarcinoma explants were treated with AL8810. Jabbour Decl. ¶ 9. Consistent with the description in the present application, these results confirm that an FP receptor antagonist can play a direct role in treating a pathological condition of the uterus, such as uterine carcinoma. *Id.* AL8810 is one of the FP receptor antagonists specifically exemplified in the patent application at page 9, lines 1-7. *Id.*

Additional data is described in the Jabbour Decl. ¶ 10, which shows that FP receptor expression is consistently higher in the endometrium of women with fibroids, during all phases of the menstrual cycle, than those without fibroids. Endometrium was collected from women with fibroids and those without, RNA was extracted from these tissues and then we assessed the level of expression of the FP receptor from the two groups of women by a technique known as reverse transcriptase polymerase chain reaction (this technique allows one to make direct comparisons of the levels of expression of the receptor in different women). *Id.* In the endometrium of women with fibroids, the level of expression of the FP receptor was consistently higher. *Id.* Taking into account knowledge of the mechanism of action of the FP receptor and its role in exacerbating vascular function, the inventors believe that antagonism of action and signaling of this elevated FP receptor in the endometrium of women with fibroids may be an effective therapeutic intervention strategy that may limit the blood loss that is associated with this pathology. *Id.* For the reasons discussed above, this gives further credibility that FP receptor antagonists are useful in treating pathological conditions of the uterus, including fibroids. *Id.*

In summary, the data presented in the present application and obtained subsequent to the filing date confirm that several uterine pathological conditions, including endometriosis, uterine carcinoma, and fibroids, all involve enhanced FP receptor expression; and, consistent with the description in the application for treating such uterine pathological conditions, treatment of uterine carcinoma explants with an FP receptor antagonist was shown to be effective in preventing FP receptor mediated expression of pro-angiogenic factors like VEGF. Jabbour Decl. ¶ 11. The results therefore confirm the efficacy of treating pathological conditions of the uterus using FP receptor antagonists. *Id.* Given the demonstrated efficacy of treating uterine carcinoma explants with an FP receptor antagonist,

persons of skill in the art would fully appreciate that a female individual having a pathological condition of the uterus, such as uterine carcinoma, endometriosis, uterine fibroids, or any other pathological conditions of the uterus that are associated with abnormal growth of the myometrium or endometrium, can be effectively treated for the condition by administering to the affected individual an FP receptor antagonist. *Id.*

Given the demonstration that the FP receptor is overexpressed in three different pathological conditions of the uterus that are associated with abnormal growth of the myometrium or endometrium, and that treatment of endometrial explants with an FP receptor antagonist can reverse the effects of PGF2α on the FP receptor, this evidence demonstrates that the claimed invention is fully supported by the present application.

For these reasons, the rejection of claims 1, 3-5, 9, 12, and 13 for lack of enablement is improper and should be withdrawn.

In view of all of the foregoing, applicants submit that this application is in condition for allowance and such allowance is respectfully requested.

Respectfully submitted,

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